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EXAMINER	
WESSENDORF, TERESA D	
ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/856,859	BATTERSBY ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,18-29,63,65 and 66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,18-29,63,65 and 66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 15, 18-29, 63 and 65-66 are pending and under examination.

Withdrawn Objections/Rejections

In view of applicants' amendments to the claims and arguments, the objection to the claims; the 35 USC 112, second paragraph rejection and 35 USC 102/103 over Lawandy and Garman rejections are withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 102

Claims 15, 18-21, 23-25, 28-29 and 63-66, as amended, are rejected under 35 U.S.C. 102 (b) as being anticipated by Egner et al (Chem. Commun., 1997)

Egner discloses at e.g., page 735, col. 1, a covalently dye beads for combinatorial synthesis of compounds tagged with fluorescence. The dye (claim 21) were covalently coupled by amide bond (claim 29) to Tentagel S-NH2 beads (130 um). The fluorescence technique was extended by the use of a laser system (light emanating of claim 1). The Tentagel beads were labeled

with florescein and erythrosin. See also Fig. 1 and Fig. 2. and Fig. 4 at page 736. Egner discloses at page 736 col. 2, that the use of colored and fluorescent beads has the potential to simplify the identification of library members for single bead screening application. Please see also the footnotes which teach the excitation of fluorescence by laser beam (claim 19).

Accordingly, the specific carrier of Egner fully meets the claimed plurality of carriers with at least two detectable features.

Response to Arguments

Applicants admit that Egner discloses spherical beads tagged with different combinations of fluorescent dyes. But argue that claim 15 is amended herein to recite that each carrier in the plurality of distinctively identifiable carriers comprises at least two light emanating features comprising a light scattering feature and a molecular fluorescence feature. While not acquiescing that Egner teaches the other elements of Claim 15, Applicants respectfully point out that the beads of Egner do not comprise both a light scattering feature and a molecular fluorescence feature.

In reply, attention is drawn to the teachings of Egner at e.g., page 735, paragraph bridging col. 1 and col. 2:

> Labeling down …….the limits were determined by the amount of background fluorescence and Raman scattering (i.e., light scattering as claim) from the bead.

Claims 15-16, 18-19, 22-25, 28-29 and 63, as amended, are rejected under 35 U.S.C. 102(b) as being anticipated by Yamashita et al (WO 95/32425)(as evidenced by Tao Jia-ping et al(Chinese Journal of Physical Medicine (Vol. 17(3), September 1995, p 168-171) and by applicants' disclosure of known prior art.)

> Yamashita discloses throughout the patent at e.g., beads which is a solid support material capable of providing a base for combinatorial synthesis such as Tentagel of 10-100 micron particles. The beads has a tag which is an encoding characteristic of a bead or groups of beads capable of being sorted by flow cytometry, such as differences in size, fluorescent marker , a fluorescent label identifier. The fluorescent label identifier is a coding label attached to a bead or group of bead either by adding ratios of a flourophor or by adding multiple, preferably two different flourophores of varying ratios. A combinatorial library containing tagged beads is shown at pages 6-9. See also page 17, lines 11-25 and page 19, Scheme 3. The multiple flourophors and linkers are disclosed at page 20, lines 5-15. See also, page 30, lines 9-16, Procedures D and E. The disclosure of Yamashita of flow cytometry inherently contains the at least two features of light scattering and fluorescence.

This is evident from the disclosure of Jia-ping bridging pages 168-169:

> …When-these different subpopulations are separated and; collected by the sorting device of a flow cytometer as depicted in Figure 1…… 4 parameters meet the requirements of e.g., light scattering, fluorescence and etc. such a technique is called four- or multi-parameter sorting technique.

Applicants' disclosure at e.g., page 52, lines 15-24 concords:

> The most common optical properties measured in a flow cytometer are forward light scatter, side light scatter and fluorescence intensity at different excitation and emission wavelengths. Of these optical properties, fluorescence offers the most potential for encoding microspheres, due to the wide variety of available fluorophores from the UV, visible or near-infra red spectrums (Haugland RP, 1996)….

See further e.g., page 22, lines 6-14 of the instant disclosure.

Accordingly, the specific carrier of Yamashita fully meets the claimed plurality of carriers with at least two detectable features.

Response to Arguments

Applicants acknowledge that Yamashita discloses uniform beads (e.g., Tentagel 10-30 micron particles, page 4 line 16) tagged by addition of combinations of fluorophores and non-fluorophores. While not acquiescing that the claims are anticipated by Yamashita, as noted above, Claim 15 is

amended herein to recite that each carrier in the plurality of distinctively identifiable carriers comprises at least two light emanating features comprising a light scattering feature and a molecular fluorescence feature. While not acquiescing that Yamashita teaches the other elements of Claim 15, Applicants respectfully point out that the beads of Yamashita do not comprise both a light scattering feature and a molecular fluorescence feature.

In reply, attention is drawn to page 20, lines 11-10 which discloses emission and fluorescence. Furthermore, the teachings of Yamashita as to the use of flow cytometry would have inherently disclosed light scattering and fluorescence (as evident from applicants' disclosure or Jia-ping of the known property of flow cytometry.)

Claims 15 and 18-21, as amended, are rejected under 35 U.S.C. 102(e) as being anticipated by Seul et al (USP 7083914) for reasons of record repeated below.

Seul et al discloses throughout the patent at e.g., col. 5, line 29 up to col. 6, line 56:

> …[c]olor codes for the purpose of uniquely labeling members of a group of beads or equivalent objects ("beads") to preserve the chemical identity of the beads and thus the

identity of bead-coupled chemical compounds. These color codes are based on a set of encoding fluorophores of distinguishable wavelengths, excited-state lifetimes and levels of intensity, the latter controlled by adjusting the abundances of dyes.

Binary and extended binary color codes offer large coding capacity and represent a general strategy to encode multi-step reaction histories such as those encountered in divide-couple-recombine (DCR) synthesis strategies for combinatorial chemical libraries.

Simple and extended simple color codes offer an efficient strategy to encode a smaller set of distinct chemistries that are typical of panels displaying multiple targets or probes in biochemical assays including multi-agent diagnostic and environmental tests and other biochemical assays.

All color codes can be augmented by varying distinguishable features of beads such as shape and size or other suitable physico-chemical parameter associated with bead cores such as polarizability.
Please see also all the drawing Figures.

Accordingly, the specific carrier of Seul et al fully meets the claimed plurality of carriers with at least two detectable features.

Response to Arguments

Applicants acknowledge that Seul discloses uniform beads (e.g., NovaSyn TG amino microspheres, col. 15, line 44) tagged by addition of combinations of fluorophores, for color coding. While not acquiescing that the claims are anticipated by Seul, as noted above, Claim 15 is amended herein to recite that each carrier in the plurality of

distinctively identifiable carriers comprises at least two light emanating features comprising a light scattering feature and a molecular fluorescence feature. While not acquiescing that Seul teaches the other elements of Claim 15, Applicants respectfully point out that the beads of Seul do not comprise both a light scattering feature and a molecular fluorescence feature.

In response, attention is drawn to col. 13, lines 20-40:

> Methods suitable for multi-spectral imaging include: multiplexing of distinct wavelengths of incident and emitted light and illumination with a superposition of multiple wavelengths, followed by dispersive imaging by means of a grating or prism (see FIG. 7) or followed by interferometric analysis of emitted light.

Attention is also drawn to the claims, e.g., claim 16:

> The method of claim 2, wherein the decoding is carried using multi-color fluorescence imaging in combination with spectral analysis.

Claims 15, 18-29, 63 and 65-66 are rejected under 35 U.S.C. 102(e) as being anticipated by Kauvar et al (USP 6642062) (as evidenced by Tao Jia-ping et al(Chinese Journal of Physical Medicine (Vol. 17(3), September 1995, p 168-171) and by applicants' disclosure of known prior art.)

Kauvar discloses throughout the patent at e.g., col. 2, line 48 up to col. 5, lines 63:

> …[a] label which comprises a particulate support to which is bound at least two signal generating moieties, which moieties generate signals that can be distinguished in situ, such as light of different wavelengths. These labels are distinguishable by any instrumentation which contains separate means for detection for each of the at least two in situ signals generated.
>
> …. [a] collection of labels wherein the ratio of the moieties differs from label to label in the collection. Typically, this collection of labels provides identifiable members that number at least twenty…. Thus, if the reliability of detection of each color is plus or minus 10 percent, 10 gray labels exist for each signal and therefore 100 hues can be distinguished when two signal generating moieties are included in each label.
> This instrumentation provides fluorescence excitation and capacity for detection of three separate wavelengths of light……Such beads are available commercially in several different colors of fluorophores with high uniformity in size and fluorophore doping levels from Flow Cytometry Standards Corp…..among others.
>
> ….[t]he number of reagents that can be separately detected under these conditions by systematic and precise doping of particulate supports with signal generating moieties, typically fluorophores, of different colors corresponding to the CCD detectors employed, at specified ratios. Particles with different ratios of the fluorophores generate different detection signals in this system. Because the ratios of the fluorophores can be varied at will, up to a point where a forced proximity of the dyes leads to quenching, many different "hues" can be generated in a collection of labeled particles, each particle type having a unique ratio and/or amount of color generating moieties.
>
> As used herein, the term "label" is generally used to describe a particulate support to which has been bound an appropriate array of signal generating moieties. The signal-generating moieties must be such that the signals

are detected in situ on the particulate support. Thus, it is unnecessary to detach the signal-generating moieties from the support in order to ascertain their ratio. Their ratio is read directly by means of the "hue" of the label. Color is a preferred signal. The labels…..contain at least two, and preferably at least three, distinguishable signal generating moieties.

As visible light is a particularly convenient way to generate a particular "hue,"… However, other signal generating moieties can be employed or an indirect method to generate visible light may be used. In addition, heavy atom clusters of different materials, for example colloidal gold dots versus ferrite rods offer different scattering characteristics with respect to electron microscope beams. The preferred "color generating" moieties are typically fluorophores, but they can also generate a characteristic wavelength either by reflectance (simple dyes) or by emission (fluorophores or de novo light-generating compounds such as a luciferase or other chemiluminescent system). A number of chemiluminescent systems are known in the art such as horseradish peroxidase-based generation of chemiluminescent products…. In addition to fluorescent dyes, phosphorescent materials may also be employed which adds the advantage that time resolved fluorescence distinguishes signals that would be equivalent averaged over a longer detection period.

The supporting particles are typically 0.1-1 .mu.m in diameter and are preferably latex. However, smaller particles may also be used. Generally, 50 nm (0.05 .mu.m) is considered an approximate minimum; it has been possible in some contexts to use particles as large as 5 .mu.m, although this is not preferred. The use of larger particles results in lower diffusion rates and thus, effectively, less efficient and less vivid labeling. A preferred range is 100-500, preferably 100-300, and more preferably 100-200 nm diameter particles. The particulate supports are generally spherical, and the microscopic techniques employed can distinguish spherical shapes from other general outlines. **Silica** gel particles may also be used. Any particulate that has suitable physical properties (does not spontaneously aggregate, adhere, or otherwise fail to behave as an independent particle) and which can be suitably derivatized with the color generating moieties and with the test reagent may be used.

> The construction of the particle itself affects the hue detected. In addition to differences attributed to the size of the particle, as indicated above, the shape will determine the nature of the signal. Shapes can vary along the continuum of sphere to oval to rod to string, for example. Star shapes or other arbitrarily shaped particles can be created by x-ray lithography so as to have a distinctive point spread function.

Accordingly, the specific carrier of Kauvar fully meets the claimed plurality of carriers with at least two detectable features.

Response to Arguments

Applicants acknowledge that Kauvar discloses using combinations of dyes, particularly fluorescent dyes, to generate multihued labels. While not acquiescing that the claims are anticipated by Kauvar, as noted above, Claim 15 is amended herein to recite that each carrier in the plurality of distinctively identifiable carriers comprises at least two light emanating features comprising a light scattering feature and a molecular fluorescence feature. While not acquiescing that Kauvar teaches the other elements of Claim 15, Applicants respectfully point out that Kauvar does not teach a synthesis support or carrier comprising both a light scattering feature and a molecular fluorescence feature.

In reply, attention is drawn again to Kauvar's disclosure above which states, for example:

> This instrumentation provides fluorescence excitation and capacity for detection of three separate wavelengths of light……Such beads are available commercially in several different colors of fluorophores with high uniformity in size and fluorophore doping levels from Flow Cytometry Standards Corp…..(as evident from applicants' disclosure or Jia-ping of the known property of flow cytometry.)

Claim Rejections - 35 USC § 103

Claims 15, 18-29, 63 and 65-66 are rejected under 35 U.S.C. 103(a) as being unpatentable over anyone of the cited references above e.g., Egner et al, Kauvar, Yamashita or Seul (hereinafter the primary references) in view of either Kris et al (USP 6238869) or Kimura et al (USP 6228480) for reasons set forth in the last office action and repeated below.

Each of Egner, Kauvar, Yamshita or Seul is discussed above. Each of these primary references does not disclose the carrier as a silica microparticle as recited in e.g., claim 27

Kris discloses throughout the patent at e.g., col. 5, lines 3-30:

> The surface (usually a solid) can be any of a variety of organic or inorganic materials or combinations thereof, including,…plastics such as polypropylene or polystyrene; ceramic; silicon; (fused) silica, quartz or glass

> microscope slide or a glass cover slip;..Substrates that are transparent to light are useful when the method of performing an assay involves optical detection….The shape of the surface is not critical. It can, for example, be a flat surface such as a square, rectangle, or circle; a curved surface; or a three dimensional surface such as a bead, particle, strand, precipitate, tube, sphere; etc.

Kimura et al discloses at e.g., col. 4, lines 15-45:

> If the adhesive layer is composed of a resin that contains colloidal silica, it is preferable if the diameter of colloidal silica particles is 10 nm or less……As a method to introduce such colloidal silica into the resin, it is known that a method to mix a resin solution with a colloidal silica solution, then apply it and subsequently dry it to form an adhesive layer is the easiest, however, a method to form an adhesive layer by allowing a resin to polymerization while dispersing colloidal silica in the resin and then to apply the synthesized resin and dry it, is also acceptable. It is also possible to use colloidal silica after treating it with a silane coupler for improving adhesive property and dispersibity of colloidal silica and a resin.
>
> As examples for a resin whereto colloidal silica is introduced, acryl resin, acryl-silicon resin, epoxy-silicon resin, silicon-modified resin, urethane resin, epoxy resin, polyester resin, alkyd resin, etc. are given, however, silicon-modified resins including acryl-silicon resin and epoxy-silicon resin, are the most suitable one in term of durability.
> As the colloidal silica, any silica sol, which is produced either by subjecting sodium silicate solution to cation exchange or by subjecting silicon alkoxide to hydrolysis, can be used.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use silica microparticle as the carrier in anyone of the primary

references as taught by either Kris or Kimura. One would have a reasonable expectation or predictable result since as Kimura or Kris teaches silica or a large number of carriers has been successfully employed in the art for combinatorial library synthesis of compounds.

Response to Arguments

Applicants submit that none of the primary references cited disclose coded carriers comprising both a light scattering feature and a molecular fluorescence feature, in accordance with the claims as amended. Kris relates to use of surfaces as substrates for attaching oligomers, and Kimura relates to surfaces comprising photocatalyst layers. Neither Kris nor Kimura relate to a plurality of carriers wherein each respective carrier has a code having at least two light emanating features comprising a light scattering feature and a molecular fluorescence feature. As such, Kris and Kimura fail to cure the deficiencies of Egner, Yamashita, Seul and Kauvar.

In reply, each of Kris or Kimura is used not for the purpose as argued. The primary references teaches carrier with at least two light emanating features. Kris and Kimura are employed for the disclosure of the advantages in the use of

silica microparticle that provides the motivation to use said silica microparticle carrier.

When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions." KSR International Co. v. Teleflex Inc., 550 USPQ2d 1385 (2007).

Thus, there is nothing new and unobvious in the claim plurality of carrier for combinatorial library synthesis wherein the multitude of carriers is coded to identify or differentiate one from the other. Coding a multitude of carrier in a library which contains millions of compounds obviously facilitates identification of the synthesized compounds in the carrier.

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/

Primary Examiner, Art Unit 1639